Drugs

2006 Limited FDA Survey of Compounded Drug Products

Executive Summary

Several studies, including a survey conducted by FDA in 2001, have reported quality problems with various pharmacy-compounded drugs, including sub-potency, super-potency, and contamination. To explore these quality issues, FDA conducted an additional survey of compounded drug products in 2006. FDA collected both active pharmaceutical ingredient (API) and finished compounded drug product samples during unannounced visits to compounding pharmacies located throughout the country. The samples were sent to FDA field laboratories for chemical analysis to measure identity of active ingredients, potency, and uniformity of dosage. The analytical methods used were generally United States Pharmacopoeia (USP) or modified-USP methods. Once all analyses were complete, FDA staff evaluated the analytical data and methods corresponding to all samples that failed at least one analytical test.

Among 198 samples gathered during FY2006, 125 were APIs and 73 were compounded finished drug products. The samples comprised three major drug classes: female hormone products, inhalation products, and local anesthetic products.

All 125 API samples passed analysis. Of the 73 compounded finished drug products, sixteen samples were not analyzed because the expiration dates on the samples elapsed before analysis. The remaining 57 samples were analyzed, but the results of the analyses for 21 of these samples were deemed unusable for various reasons and excluded from the survey. Of the remaining 36 samples, 12 (33%) failed analytical testing using rigorously defensible testing methodology.

Most of the products that failed analysis did so due to sub or super-potency, called assay, or a lack of uniformity of individual dosage units, called content uniformity. Potency ranged from 67.5% to 268.4% of the amount of drug declared on the product labeling. For content uniformity analysis of products containing multiple active components, both sub- and super-potent active components were found within the same product samples. Such variability can lead to uncertainty in dosing and raises concern for patient therapy.

The results of the survey suggest that problems with the quality of compounded drugs occur throughout the country. Of note is that all APIs passed analytical testing, supporting the notion that the observed failures of the finished drug products may be causally related to the compounding processes at pharmacies.

Introduction

FDA regards traditional pharmacy compounding as the extemporaneous combining, mixing, or altering of ingredients by a pharmacist in response to a physician's prescription to create a medication tailored to the specialized medical needs of an individual patient. Traditional compounding typically occurs when an FDA-approved drug is unavailable or a licensed health-care provider decides that an FDA-approved drug is not appropriate for his or her patient's medical needs. By definition, pharmacy compounding involves making a new drug for which safety and efficacy have not been demonstrated with the kind of data that FDA requires to approve a new drug. In virtually all cases, FDA regards compounded drugs as unapproved new drugs.

The unapproved status of compounded drugs notwithstanding, FDA has long recognized that traditional pharmacy compounding serves an important public health function. FDA has historically exercised enforcement discretion and generally has not taken enforcement action against pharmacies engaged in traditional compounding. Rather, FDA has directed its enforcement resources toward firms that manufacture large quantities of unapproved new drugs under the guise of traditional compounding, and whose compounding practices result in significant violations of the new drug, adulteration, or misbranding provisions of the FDCA.

Improperly compounded, adulterated drugs have the potential to cause significant harm to patients. From 1990 to 2005, FDA learned of at least 240 serious illnesses and deaths associated with improperly compounded products. Because pharmacists are not required to report adverse events to FDA, there may be additional deaths and injuries of which the agency is unaware. There are also reports in the literature of serious injuries, some involving children, caused by improperly compounded products. For instance, two cases of hospitalization of children occurred due to compounded preparations that were 10-fold and 87-fold superpotent.[1] In another case, pharmacy mixing of a medicine too long before use, allowing chemical generation of a toxin, was suggested to have a role in the death of a patient.[2] Finally, a retrospective review of patient records at a poison control center for a 35 month period found three overdoses, two involving medications for children, related to compounded drugs.[3] These cases illustrate that the quality problems associated with compounded drug products can have serious and fatal consequences for patients.

FDA is aware of a number of product quality problems associated with compounded drugs including contamination, poor compounding processes, and product toxicity.[4] In 2001, FDA conducted limited sampling of compounded drug products purchased over the Internet.[5] This preliminary study showed that 9 of 29 samples analyzed (31%) were sub-potent, ranging from 59% to 89% of the labeled value. Issues with product potency have been observed in other studies and surveys. For example, Azarnoff et al.[6] filled prescriptions for 0.3% nitroglycerin ointment and, upon analysis, found that 29% of the 24 samples were subpotent and one sample was superpotent. This product was widely used, as it was reported that 84,000 prescriptions for this ointment were written in 2004. In another survey, compounded drug testing conducted by the Missouri State Board of Pharmacy demonstrated failure rates ranging from 19.8% to 25.2% of all compounded drugs tested, including samples that contained 0.0% to 553% of the product's labeled potency.[7]

The cause of errors in compounding leading to incorrect potency is not well understood, but such compounding errors can be observed during pharmacy student training. Kadi and colleagues[8] examined the accuracy of the compounding of two simple solutions by pharmacy students. For one of the solutions, only 54% of students prepared the medications within 10% of the desired concentration. Errors for the remaining mixtures ranged from less than 75% to greater than 200% of the desired concentration. Results for the second solution showed 78% of students within +/- 10% of the desired concentration, however, the range of concentration errors was greater (-89% to 269%).

In addition to incorrect potency, contamination of compounded finished drug products has also been observed. Contamination can manifest as either microbial contamination or the presence of chemical impurities. Several studies have shown that both incorrect potency and contamination can exist within the same products. Goldman[9] conducted an analysis of solutions of sodium tetradecyl sulfate from three compounding pharmacies and found that the dosage forms failed to meet labeled concentrations. The analysis also detected the presence of the contaminant carbitol in each sample. In another study, Mahaguna and colleagues[10] reported the analysis of compounded progesterone suppositories from 10 randomly selected pharmacies throughout the United States. According to the study, 9 of 10 pharmacies provided suppositories that fell outside potency limits set for approved products. In addition, one

pharmacy provided suppositories testing positive for *Comamonas acidovorans* bacteria. Another study, by Sarver et al,[11] found that 18% of extemporaneously compounded samples of alprostadil for injection tested positive for microbial contamination. In addition, 23% of samples had alprostadil concentrations of greater than +/- 10% of their labeled amount.

The quality problems encountered with compounded finished drug products are magnified by their extensive use. In a survey of independent community pharmacies in Illinois, Missouri, Kansas, and Iowa, 94% of pharmacies reported that 2.3% of their dispensed prescriptions were compounded.[12] On a nationwide basis, one percent of all prescriptions, totaling approximately 30 million, were estimated to be compounded in 2003.[13] Given the widespread occurrence of pharmacy compounding and the potential for serious injury resulting from the use of improperly compounded products, the quality of compounded drugs creates an important public health concern.

Methods

The present survey was designed collaboratively by FDA's Center for Drug Evaluation and Research, Office of Compliance, and FDA's Office of Regulatory Affairs. FDA staff compiled a list of compounded drugs that are both commonly used and likely to be available at compounding pharmacies, in addition to compounded drugs that could be associated with quality or compounding problems. Investigators obtained samples of both APIs and finished compounded drugs from compounding pharmacies located throughout the country. Most pharmacies were chosen from a list of compounding pharmacies that was created from the Internet and telephone directories. The samples were sent to FDA field laboratories for analysis.

The samples were analyzed for identification of active ingredient as well as potency, or assay, of ingredients declared in the product labeling. If the compounded finished product was in capsule form, the capsules were analyzed for content uniformity. The analytical methods were from the United States Pharmacopeia (USP). High pressure liquid chromatography was generally used to quantify the amount of active drug substances present (titration was used once). Failure of a sample to meet USP specifications for the drug as labeled was confirmed with an additional analysis, known as a "check analysis," by a second chemist. Any analyses that occurred past the labeled date of expiration were considered invalid. The collection reports and laboratory analysis results were entered into FDA's database of field activities: the Field Accomplishments and Compliance Tracking System (FACTS).

Documentation in FACTS was retrieved for summarization. All analytical worksheet documentation for drug samples failing USP specifications was collected and scrutinized. Based on the quality of the analytical data, the laboratory analysis for each sample that failed analytical testing was classified as acceptable (i.e., scientifically rigorous) or unacceptable.

Results

FDA collected 125 API samples and 73 compounded finished product samples from pharmacies located throughout the United States (Table 1). The samples encompassed three major therapeutic areas: local anesthetic products, inhalation products, and female hormone products. Both the finished compounded drug products and the APIs were analyzed as described in the Methods section. Table 2 summarizes the results of the laboratory analyses. All 125 of the APIs passed laboratory analysis for both the identity of the active drug substance and assay for the amount of active drug substance present.

Of the 73 compounded finished drug products, sixteen samples were not analyzed because the expiration dates on the samples elapsed before analysis. The remaining 57 samples were analyzed, but the results of the analyses for 21 of these samples were deemed unusable for various reasons and excluded from the survey. Of the remaining 36 samples, 12 (33%) failed analytical testing using rigorously defensible testing methodology (Table 2).

The compounded finished drug products that were analyzed included different formulations and fell into three therapeutic classes: female hormones, local anesthetics, and inhalation drugs. Analysis results for these products, categorized by both formulation and therapeutic class, are described in Table 3. Three local anesthetic products failed analysis. For female hormone products, 9/31 (29%) failed analysis. Two inhalation products were tested and passed analysis.

The failed samples passed identity testing but failed assay and, in some cases, content uniformity testing. Content uniformity testing was only performed on compounded finished products in capsule form. Table 4

summarizes the number of products for each formulation that failed testing and whether the samples failed assay testing, content uniformity testing, or both. All products that failed at least one analytical test failed assay testing, suggesting inadequate potency, and the vast majority of capsules failed content uniformity testing. Potency ranged from 67.5% to 268.4% of the amount of drug declared on the product labeling.

Capsules with content uniformity problems often exhibited potency variations with respect to more than one active component. It was possible to find both sub-potent and super-potent active components within the same sample. Figure 1 illustrates the content uniformity observed in a sample in which capsules appear to contain super-potent concentrations of estrone and sub-potent concentrations of estriol and estradiol.

Discussion

These data reflect significant problems with the quality of certain compounded drugs. The analysis of compounded finished drugs revealed instances of unreliable potency and, in the case of products in capsule form, unreliable uniformity of dosage. The observed potencies of the finished drug products were widely variable, ranging from 67.5% to 268.4% of the labeled potency. For capsules, both sub- and super-potent active components were found in the same product samples. Variability in potency can lead to uncertainty in dosing and raises concerns for patient therapy.

All of the API samples passed analytical testing, suggesting that the failures of the compounded finished drug samples were related to compounding processes at the pharmacies. Previous studies suggest that seemingly straightforward preparation of certain drugs may present significant challenges in pharmacy settings,10 particularly when proper in-process controls and end-product testing are not in place to monitor and ensure dosage quality and uniformity.13 For instance, the uniformity of multi-component solid oral dosage forms relies on achieving homogeneity of a powder mixture prior to encapsulation. This process of mixing a multi-component product is scientifically complex and may be influenced by numerous factors including, but not limited to, the physical and chemical properties of the ingredients and their interactions with each other, properties of the mixing container, speed of mixing, temperature, and humidity.[14, 15, 16, 17, 18]

Some samples were excluded from the study for procedural and methodological reasons. These include sixteen products that were not analyzed because they reached their labeled expiration date prior to analysis. In addition, 21 samples failed analysis, but were excluded due to one or more of the following methodology problems: the samples had expired when tested, the expiration date passed before check analysis could be performed, the analytical method was technically poor, or the sample passed the check analysis after failing initial testing (Table 5).

The limitations of this survey included resource constraints and issues related to laboratory analysis. During laboratory analysis, there were instances when methodology development and validation were needed to accurately analyze the samples. Because the samples were collected in limited quantities, this was not always possible. In those instances, the test results were excluded from the survey. In addition, potency, identity, and content uniformity were each assessed with a single analytical technique. The fact that no secondary analytical methods were used for the sample analyses reflects the informational nature of the survey.

Conclusions

Poor quality compounded drugs are a serious public health concern, as improperly compounded products have been linked to grave adverse events, including deaths. The results of the FY 2006 compounded drug survey suggest a problem with the quality of certain compounded drug products. All of the API samples passed analytical testing, suggesting that the analytical failures of the finished drug products were likely related to the compounding processes at the pharmacies. Thirty-three percent of compounded finished product samples did not conform to product labeling in terms of potency and/or content uniformity. The majority of the finished compounded product samples analyzed in this survey were hormone therapy products. These products appear to be popular, commonly compounded, and available at many pharmacies. Given the wide use of these products, the fact that nearly one-third failed analytical testing raises public health concerns. The potencies of the compounded finished drug products that failed analysis were highly variable and, in the case of content uniformity, both sub- and super-potent active components

were found in the same product samples. The wide range in potency and uniformity of dosage observed in this survey can, in a clinical setting, lead to uncertainty in the amount of drug that a patient receives. Such uncertainty can lead to medication errors that pose a health risk for patients who rely on compounded drugs.

Tables and Figures

Table 1. Active Pharmaceutical Ingredients and Finished Compounded Drug Products Collected for the FY 2006 Compounded Drugs Survey

Pharmacy Code, State	Active Ingredients	Dosage Form
AA, NC	Estriol, Estradiol	Capsules
AA, NC	Estriol, Estradiol, Estrone	Capsules
AA, NC	Progesterone	API
AB, MN	Estriol	API
AC, NC	Estradiol	API
AC, NC	Progesterone	API
AC, NC	Tetracaine HCl	API
AD, NC	Lidocaine	API
AD, NC	Lidocaine, Tetracaine	Gel, topical
AD, NC	Progesterone	Cream
AD, NC	Progesterone	API
AD, NC	Tetracaine	API
AE, GA	Lidocaine	Spray, throat
AE, GA	Lidocaine HCl	API
AE, GA	Progesterone	API
AE, GA	Tetracaine HCl	API
AF, NC	Progesterone	Capsules
AF, NC	Estriol	API
AF, NC	Lidocaine	API
AG, NC	Albuterol sulfate	API
AG, NC	Ipratropium bromide	API
AG, NC	Lidocaine	API
AG, NC	Progesterone	API
AH, NC	Progesterone	Capsules
AI, VA	Estradiol	API
AI, VA	Estriol	API
AI, VA	Lidocaine	API
AI, VA	Progesterone	Capsules
AI, VA	Progesterone	API
AJ, VA	Estriol, Estradiol, Estrone, Progesterone	Capsules, sustained release
AJ, VA	Progesterone	Capsules, sustained release
AK, WV	Progesterone	API
AL, VA	Estriol, Estradiol	Capsules
AM, MD	Estradiol	API
AM, MD	Progesterone	API
AN, VA	Estriol, Estradiol	Capsules
AN, VA	Progesterone	Capsules, sustained release
AO, VA	Estradiol	Cream
AP, MD	Lidocaine	API
AP, MD	Progesterone	API
AQ, VA	Progesterone	API
AR, IL	Estradiol	API
AR, IL	Estriol, Estradiol	Capsules
AR, IL	Progesterone	API
AR, IL	Progesterone	Capsules, sustained release
AS, OH	Estriol, Estradiol	Capsules

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AS, OH	Estriol, Estradiol, Progesterone	Capsules
AS, OH	Progesterone	Capsules
AT, KY	Progesterone	API
AU, MN	Tetracaine	API
AV, OH	Lidocaine	API
AV, OH	Progesterone	API
AW, OH	Estadiol	API
AW, OH	Estriol, Estradiol	Capsules
AW, OH	Progesterone	Capsules
AW, OH	Progesterone	API
AX, OH	Estriol, Estradiol	Capsules
AX, OH	Estriol, Estradiol, Estrone	Capsules
AX, OH	Progesterone	Capsules
AY, OH	Estrone	API
AY, OH	Estriol, Estradiol, Estrone	Capsules
AY, OH	Progesterone	API
AZ, OH	Lidocaine	API
AZ, OH	Lidocaine	API
AZ, OH	Progesterone	API
BA, OK	Estriol, Estradiol	Capsules
BA, OK	Progesterone	Capsules, sustained release
BB, OK	Lidocaine HCl	API
BB, OK	Progesterone	API
BC, MI	Estriol	API
BC, MI	Estrone	API
BC, MI	Lidocaine	API
BC, MI	Progesterone	API
BC, MI	Tetracaine	API
BD, MI	Estriol, Estradiol	Capsules
BD, MI	Estriol, Estradiol, Estrone	Capsules
BD, MI	Lidocaine	API
BD, MI	Progesterone	Capsules
BD, MI	Progesterone	API
BD, MI	Progesterone	Suppositories
BD, MI	Tetracaine	API
BE, MI	Estradiol	API
BE, MI	Estriol	API
BE, MI	Estriol, Estradiol	Capsules
BE, MI	Estriol, Estradiol, Estrone	Capsules
BE, MI	Estriol, Estradiol, Progesterone	Capsules
BE, MI	Progesterone	Capsules
BE, MI	Progesterone	API
BF, MI	Estradiol	API
BG, FL	Estradiol	API
BG, FL	Estriol	API
BG, FL	Progesterone	API
BH, FL	Lidocaine HCl	API
BH, FL	Progesterone	API
BI, FL	Lidocaine	API
BI, FL	Progesterone	API
BI, FL	Tetracaine	API
BJ, FL	Albuterol sulfate	API
BJ, FL	Progesterone	API
BK, CA	Estriol, Estradiol, Estrone	Capsules
BL, AZ	Estradiol	Cream
BL, AZ	Estradiol	API

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		Lidocaine	Gel
BL, AZ		Lidocaine	API
BM, CA		Lidocaine	API
BM, CA		Progesterone	API
BN, CA		Estradiol	Cream
BN, CA		Progesterone	API
BO, CA		Estradiol	API
BO, CA		Estriol	API
BO, CA		Lidocaine	API
BO, CA		Progesterone	API
BO, CA		Tetracaine	API
BP, CA		Estriol	API
BP, CA		Estrone	API
	BQ, CA	Estriol, Estradiol	Capsules
	BR, AZ	Estradiol Cypionate	API
	BS, MN	Lidocaine	API
BS, MN		Progesterone	API
BS, MN		Tetracaine	API
	BT, ND	Estriol, Estradiol, Progesterone	Capsules, sustained release
BT, ND		Progesterone	Capsules
BT, ND		Progesterone	Capsules, sustained release
	BU, WI	Estriol, Estradiol, Estrone	Capsules
	BV, WI	Progesterone	Capsules, hard gel
BV, WI		Progesterone	Capsules, hard gel
BV, WI		Progesterone	Capsules, hard gel
	BW, ND	Estriol, Estradiol	Capsules, sustained release
BW, ND		Lidocaine	API
BW, ND		Tetracaine	API
	BX, WI	Estriol, Estradiol	Capsules
BX, WI		Progesterone	Capsules, sustained release
BX, WI		Progesterone	API
	BY, MN	Lidocaine	API
BY, MN		Progesterone	API
	BZ, CT	Albuterol sulfate	API
BZ, CT		Ipratropium bromide	API
	CA, CT	Estradiol	API
CA, CT		Lidocaine	API
CA, CT		Lidocaine HCl	API
CA, CT		Progesterone	API
CA, CT		Tetracaine HCl	API
	CB, MN	Albuterol sulfate	API
	CC, MA	Estrone	API
CC, MA		Progesterone	Suppositories, vaginal
	CD, ME	Estradiol	Capsules, oil
CD, ME		Lidocaine, Dexamethasone	Gel
CD, ME		Progesterone	Capsules
CE, NH		Lidocaine HCl	API
CE, NH		Progesterone	API
CE, NH		Tetracaine	API
	CF, NH	Progesterone	API

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CG, NJ	Estradiol	Cream
CG, NJ	Estriol, Estradiol	Capsules
CG, NJ	Estriol, Estradiol, Estrone	Capsules
CG, NJ	Estriol, Estradiol, Progesterone	Capsules
CH, NJ	Lidocaine HCl	API
CI, NJ	Estriol	API
CI, NJ	Progesterone	Capsules
CJ, NJ	Estrone	API
CJ, NJ	Progesterone	API
CJ, NJ	Progesterone	Capsules, sustained release
CJ, NJ	Tetracaine HCl	API
CK, NJ	Lidocaine HCl	API
CK, NJ	Progesterone	API
CL, NJ	Progesterone	API
CL, NJ	Tetracaine	API
CM, NJ	Estriol, Estradiol, Estrone	Capsules
CM, NJ	Estriol, Estradiol, Progesterone	Capsules
CM, NJ	Progesterone	Capsules
CM, NJ	Progesterone	Injectable
CN, FL	Progesterone	API
CO, NY	Estriol	API
CO, NY	Lidocaine	API
CO, NY	Progesterone	API
CO, NY	Tetracaine	API
CP, NY	Estriol	API
CP, NY	Estriol, Estradiol, Estrone, Progesterone	Capsules, modified release
CP, NY	Estriol, Estradiol, Progesterone	Capsules
CP, NY	Lidocaine	API
CP, NY	Progesterone	Capsules
CP, NY	Progesterone	API
CQ, NY	Progesterone	API
CQ, NY	Tetracaine	API
CR, NY	Lidocaine	API
CR, NY	Progesterone	API
CS, PA	Progesterone	Capsules, sustained release
CS, PA	Progesterone	API
CT, PA	Albuterol sulfate	API
CU, CA	Progesterone	Capsules
CV, CA	Progesterone	Capsules
CW, CA	Progesterone	Capsules
CX, PR	Albuterol sulfate	API
CX, PR	Ipratropium bromide	API
CX, PR	Ipratropium, Albuterol	Inhalation solution
CY, PR	Albuterol sulfate	API
CY, PR	Ipratropium bromide	API
CY, PR	Ipratropium, Albuterol	Inhalation solution

Table 2. Results of Laboratory Analysis for all Survey Samples

Category	Type of Drug: Compounded Finished Product	Type of Drug: Active Pharmaceutical Ingredient
Total	**73**	**125**
Passed	24	125

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Failed	12	
Failed, analysis unacceptable *	21	
Never analyzed because sample expired*	16	
Failed	12/36 = (33%)	0/125 (0%)

* Samples excluded from survey

Table 3. Analysis Results of Compounded Finished Drug Products Categorized by Formulation and Therapeutic Class

Active Ingredients	Dosage Form	Therapeutic Class (H = Hormone, LA = Local Anesthetic I= Inhalation)	Passed	Failed
Total (36 samples)			**24**	**12**
Estradiol	Cream	H	2	1
Estriol, Estradiol	Capsules	H	1	4
Estriol, Estradiol, Estrone	Capsules	H	1	3
Estriol, Estradiol, Progesterone	Capsules	H	1	1
Progesterone	Capsules	H	3	
Progesterone	Capsules, sustained release	H	13	
Progesterone	Cream	H	1	
Ipratropium, Albuterol	Inhalation solution	I	2	
Lidocaine	Throat spray	LA		1
Lidocaine	Gel	LA		1
Lidocaine, Tetracaine	Topical Gel	LA		1

Table 4. Compounded Finished Products that Failed Assay for Potency or Content Uniformity

Product	Dosage Form	Assay	Content Uniformity
Estradiol	Cream	1	N/A
Lidocaine	Throat spray	1	N/A
Lidocaine	Gel	1	N/A
Lidocaine, Tetracaine	Topical Gel	1	N/A
Estriol, Estradiol	Capsule	4	0*
Estriol, Estradiol, Estrone	Capsule	3	3
Estriol, Estradiol, Progesterone	Capsule	1	1

* Four products failed initial testing, but check analyses were not performed, samples excluded

Figure 1. Lack of Uniformity of Dosage for Capsules Containing Multiple Active Components

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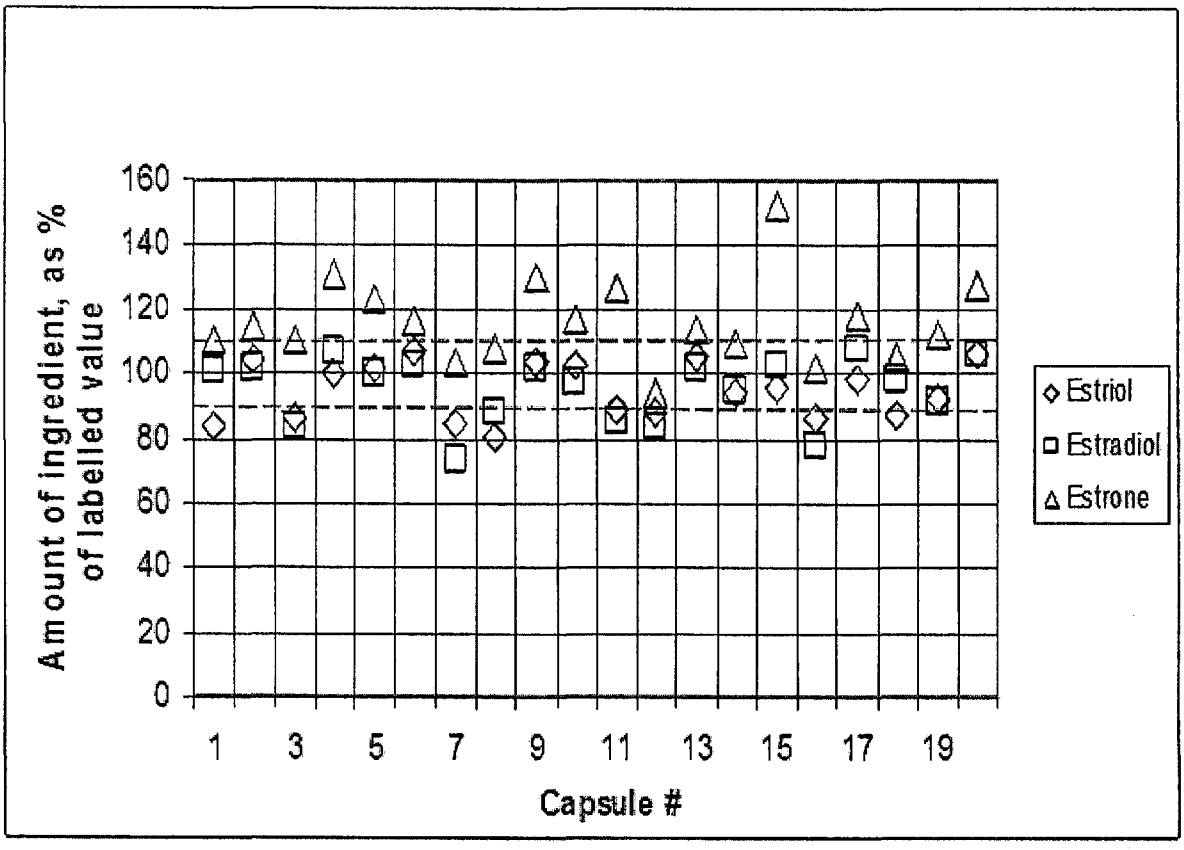

Table 5. Characterization of Methodology Issues Encountered During FY 2006 Compounded Drugs Survey (Samples could meet more than one criterion.)

	Reason Analysis Was Classified as Unacceptable			
Total Samples	**Sample Expired**	**No Check Analysis**	**Problem with Analytical Process**	**Sample Passed Check Analysis**
21	2	11	11	1

Acknowledgments

Contributors to the study include individuals from numerous FDA units described below:

Survey design: Compounded Drugs Team, Division of New Drugs & Labeling Compliance, Office of Compliance, Center for Drug Evaluation and Research (CDER)
Survey assignment development: Surveillance Programs Team (SPT), Division of Compliance Risk Management and Surveillance, Office of Compliance, CDER
Sample collection: 15 Districts in Office of Regulatory Affairs (ORA) –

- Atlanta
- Baltimore
- Chicago
- Cincinnati
- Dallas
- Detroit

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- Florida
- Los Angeles
- Minneapolis
- New England
- New Jersey
- New York
- Philadelphia
- San Francisco
- San Juan

Laboratory assignments and laboratory worksheet review: Division of Field Science, ORA
Laboratory analysis: 9 Laboratories in ORA –

- Denver District
- Detroit District
- Kansas City District
- Northeast Regional
- Philadelphia District
- Pacific Regional – Northwest (Seattle)
- Pacific Regional – Southwest (Los Angeles)
- San Juan District
- Southeast Regional

Data assembly, analysis, interpretation, and report: SPT.

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Silver Spring, MD 20993
Ph. 1-888-INFO-FDA (1-888-463-6332)
Email FDA

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